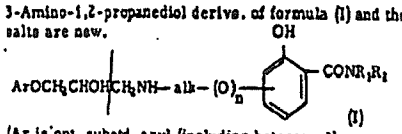
68119 C/39 805 CIBA 01.03.79
CIBA GEIGY AG *EP-15-505
01.03.79-CH-002037 (17.09.80) C07c-103/26 C07c-125/06 C07c-127/15 C07c-147/06 C07c-149/18

3-amino-1,2-propane-diol 1-aryl ether derivs. - used as beta-adrenergic blockers or stimulants for treating cardiac disorders

D/S: E(BE, CH, DT, FR, GB, IT, LU, NL, OE, SW).

3-Amino-1,2-propanediol derivs. of formula (I) and their salts are new.



(I)

(Ar is opt. substd. aryl (including heteroaryl);
n is 0 or 1;
alk is 2-5C alkylene with ⩾ 2C in the chain between the NH and the phenyl or phenoxy gp.;
R_1 and R_2 are each H or lower alkyl; or they together form lower alkylene opt. interrupted by O, S, N or N-lower alkyl).

USES

Some cpds. (I), esp. those with Ar = hydroxyphenyl, have β-adrenergic stimulant activity with high selectivity for cardiac (β_1) receptors. They can be used as positive inotropic agents, esp. as cardiotonics for treating cardiac muscle insufficiency (opt. in combination with cardiac glycosides etc.), and also for treating cardiac rhythm disorders. Dose is 0.01-1 mg/kg p.o.

Other cpds. (I) have β-blocking activity, possibly with intrinsic sympathomimetic activity. Cpds. with a p-substituent show good cardiac selectivity, while cpds. with an o-substituent have less cardiac selectivity and also have α-blocking activity. The β-blocking cpds. can be used for treating angina pectoris and arrhythmia, and as hypotensives. Dose is 0.03-3 mg/kg p.o.

(I) are also intermediates for other cpds., esp. drugs.

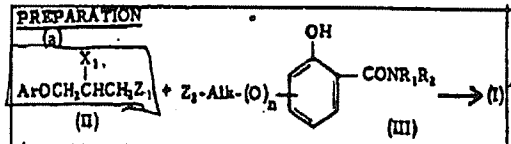
SPECIFICALLY CLAIMED

18 Cpds. (I), e.g. 1-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethylamino]-3-[4-(2-methoxyethoxy)-phenoxy]-2-propanol; 4-[2-hydroxy-3-[(3-carbamoyl-4-hydroxy-phenoxy)-ethylamino-propoxy]-phenylacetamide; 1-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethylamino]-3-[2-(pyrrol-1-yl)-phenoxy]-2-propanol; 1-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethylamino]-3-(2-methyl-indol-4-yloxy)-2-propanol; and 5-[3-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethylamino]-2-hydroxy-propoxy]-1,2,3,4-tetrahydro-2,3-cis-naphthalene-diol. EP--15505+

68119C

PREPARATION

(a)



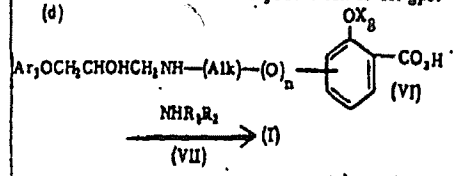
(II) (III)

(one of Z_1 and Z_2 is reactively esterified OH, the other is NH_2 and X_1 is OH; or X_1 and Z_1 together are epoxy and Z_2 is NH_2).

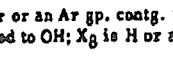
(b) Precursors with protected hydroxy gps. can be deprotected to give (I).

(c) Imino (Schiff base) precursors with =N- or -N= in the side-chain instead of -NH- can be reduced to (I), opt. with simultaneous reductive deprotection of OH gps.

(d)



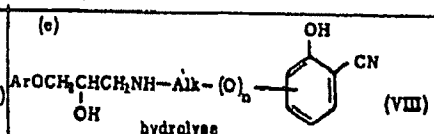
(VI)



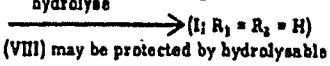
(VII) (I)

(Ar_3 is as Ar or an Ar gp. contg. 1 or 2 gps. which can be aminolysed to OH; X_8 is H or an aminolysable protecting gp.)

(e)



(VIII)



(I; $R_1 = R_2 = H$)

OH gps. in (VIII) may be protected by hydrolysable gps.

EXAMPLE

A mixt. of 11.2 g 1-(2-allyloxy-phenoxy)-3-amino-2-propanol, 10.5 g 5-(2-oxo-propoxy)-salicylamide, 200 ml toluene and a few drops of acetic acid was refluxed until water sepn. ceased (2-3 hrs.). The residue was dissolved in 300 ml EtOH. 5.7 g $NaBH_4$ was added in portions with stirring. The mixt. was stirred 2 hrs. at 20-30°C, left to stand overnight, adjusted to pH 3-4 with HCl, filtered and evapd. The residue was partitioned between 100 ml water and 100 ml EtOAc. The aq. phase was made alkaline with NH_4OH and extd. with 200 ml EtOAc. The organic phase was worked up to give an enantiomer mixt. of 1-(2-allyloxy-phenoxy)-3-[2-(3-carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethylamino]-2-propanol as an oil. Slow crystn. from i-PrOH gave the pure enantiomer pairs, m. pt. 123-125°C and 98-102°C. (91pp961). (G) FGR: DE2032642; DT2357849. EP--15505